SOME QUANTITATIVE METHODS FOR THE STUDY OF SPONTANEOUS ACTIVITY OF SINGLE NEURONS

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ABSTRACT Four different illustrative examples of single unit data from the cochlear nucleus of anesthetized cats are presented. The spontaneous activity of each of these four units can be quantitatively described by the histogram of interspike intervals and by other related measurements. Several descriptive models are suggested by these measurements.

INTRODUCTION

Spontaneous electrical activity, the activity that is observed in the absence of experimentally introduced stimui, has long been of interest to students of the nervous system. Various widely divergent opinions have been expressed concerning the functional significance of such activity (Lowenstein and Sand, 1940), (Bremer, 1953), (Granit, 1955), (Kuffler, FitzHugh, and Barlow, 1957), (Schlag, 1959). These views range all the way from depicting spontaneous activity as merely "noise" in the nervous system, to considering it as a carrier that is modulated to transmit information.

Regardless of one's speculations about the function of spontaneous activity, one may study it in a completely operational way by describing its statistical characteristics. In this paper we shall present some systematic procedures that may be used in the study of spontaneous spike activity of single units. One of the particular measurements, the interval histogram, has been used previously to describe the statistical properties of a sequence of spontaneous nerve impulses recorded from isolated axons in specific chemical environments or from relatively intact preparations. (Brink, Bronk, and Larabee, 1946), (Hagiwara, 1954), (Kuffler, FitzHugh, and Barlow, 1957). The present paper can be regarded as an extension of these earlier attempts to quantify the statistical nature of neural discharge.

We have chosen the cochlear nucleus as the general site for our study, since it is small, delimited, accessible, relatively peripheral, and contains many types of cells. Relatively detailed anatomical descriptions are available (Ramón y Cajal, 1909), (Lorente de Nó, 1933). In addition, some knowledge exists concerning responses of single units in this region to acoustic stimuli (Galambos and Davis, 1943), (Tasaki and Davis, 1955), (Rose, Galambos, and Hughes, 1959), (Grossman and Viernstein, 1961). It should be emphasized, however, that this paper is not intended to be a survey or catalog of unit spontaneous activity in the cochlear nucleus, but to be a description of certain methods that are applicable to the study of unit spontaneous activity in general, with illustrative examples taken from single units in the cochlear nucleus.

METHODS

Experimental Methods. All of our experiments were performed on cats that were anesthetized intraperitoneally with Dial (75 mg/kg). Most of the experiments lasted for 12 to 18 hours; no supplementary anesthesia was given. The cochlear nucleus on one side was exposed by partially removing the cerebellum. Electrodes of the indium-platinum type as described by Dowben and Rose (1953) and modified by Gesteland, Howland, Lettvin, and Pitts (1959) were inserted in the cochlear nucleus. We have been able to locate the site of the recording electrodes only in a gross way. Most of the units reported here were in either the anterior or posterior ventral cochlear nucleus.

All of the recording was done with the cat in a shielded soundproof chamber. In most of the experiments the round-window responses to acoustic stimuli were checked to establish the "normality" of the preparation. Acoustic stimuli were delivered by a TDH-39 (10 ohm) earphone connected to hollow ear bars of the headholder by a plastic tube. Most of the units reported here responded to appropriate sounds.

The spike discharges of single units were recorded on magnetic tape. Units selected for study had to meet the following criteria:

(*a*) The spikes had to be initially negative in polarity with reference to the headholder.
(*b*) The spikes had to remain stable in rate with small advancements of the electrode.
(*c*) The spikes had to be sufficiently well isolated from other activity so that a level detector would be activated only by the spikes of the unit that was under study.

Computational Methods. The spikes selected by the level discriminator were fed directly to the TX-O digital computer, which had been programmed to perform these analyses:

(a) Interval histogram—a histogram of the distribution of intervals between successive spikes. This analysis is illustrated schematically in Fig. 1a.

(b) Joint interval histogram—a histogram of the joint distribution of two successive interspike intervals. This analysis is illustrated in Fig. 1b.

(c) Scaled interval histogram—a histogram of the intervals between every $2^{m\text{th}}$ spike, where m is an integer. (For $m = 0$ this is identical to the interval histogram). This analysis is illustrated in Fig. 1c for three values of m.

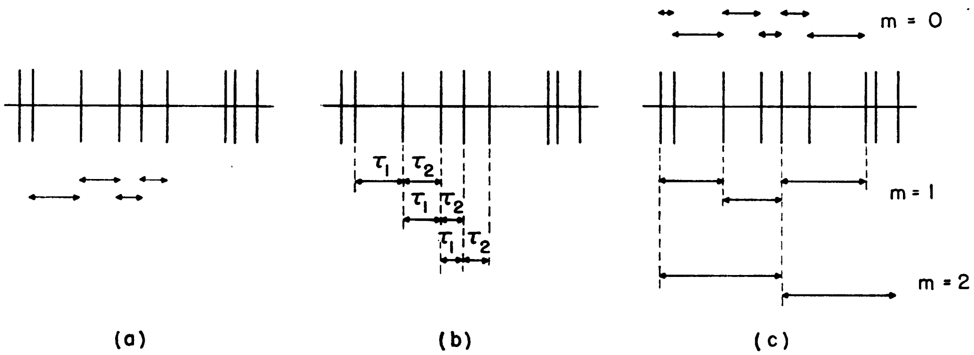

FIGURE 1 Diagram illustrating the computations used in this paper. (a) Interval histogram; (b) Joint interval histogram; (c) Scaled interval histogram of order m.

The results of these analyses appear as displays on the computer-controlled oscilloscope and are photographed. For the ordinary interval and scaled interval histograms the display is in the form of a bar graph (128 bars). The abscissa represents the duration of the time interval; the ordinate represents the number of intervals whose duration falls between τ and $\tau + \Delta\tau$. The $\Delta\tau$ is called the bin width and determines the time resolution of the analysis. For convenience in describing the shape of histograms, we shall frequently use such terms as "rise" and "decay" to describe the envelopes. This terminology in no way implies a time ordering of the events described by the histogram.

Joint interval histograms are displayed as two-dimensional plots: the abscissa represents duration of τ_1, the first of the pair of intervals; the ordinate represents duration of τ_2, the second of the pair of intervals. The number of interval pairs which has occurred with particular (τ_1, τ_2) values is represented by the intensity of the spot at coordinates (τ_1, τ_2).

The analyses described above can be explained more precisely and formally. This has already been done for interval histograms (Gerstein and Kiang, 1960). We shall use similar notation here.

Let the spike train be represented by

$$f(t) = \sum_{k=0}^{N} \delta(t - t_k), \tag{1}$$

where $\delta(t)$ is a Dirac delta function, and N is a large number. Each δ-function (of unit area) is located at the time of a spike in the original train. The interval histogram (of the intervals between successive spikes) may then be written

$$I(\tau) = \sum_{k=1}^{N} \delta(t_k - t_{k-1} - \tau). \tag{2}$$

It is often convenient to measure the continuous values of τ as discrete time values τ_j, $j = 1, 2, 3, \ldots$, in such a way that all τ that satisfy $\tau_j \leq \tau < \tau_{j+1}$ are measures τ_j. Thus $\tau_{j+1} - \tau_j = \tau$ defines a time bin width that determines the resolution of the analysis. For discrete time, the areas of all δ-functions of equation (2) which fall between τ_j and τ_{j+1} are added together to give the height of the τ_j^{th} bar in a histogram.

Although the shape of the interval histogram does provide a method of characterizing some features of spike trains, as shown below, all of the information about the time ordering of particular intervals is necessarily lost.

A particular aspect of such time ordering is the relationship between successive time intervals (Gerstein, 1961). This may be investigated by computing the estimator of the joint probability density for successive time intervals, that is, the joint interval histogram.

Formally, we write

$$I(\tau_1, \tau_2) = \sum_{k=2}^{N} \delta(t_{k-1} - t_{k-2} - \tau_1)\, \delta(t_k - t_{k-1} - \tau_2). \tag{3}$$

Here, $I(\tau_1, \tau_2)$ is related to the probability of finding an interval τ_1 followed by an interval τ_2. In a formal sense, the restriction to successive time intervals is arbitrary. We would, however, expect correlation between two intervals only if they are close together in time. A joint interval histogram for two intervals that are relatively far apart in time should show complete independence.

Note that the joint interval histogram can be simply related to the ordinary interval histogram in the following manner:

$$\sum_{\text{all } \tau_2} \frac{1}{N^2}\, I(\tau_1, \tau_2) = \frac{1}{N}\, I(\tau_1), \tag{4}$$

in which we have considered the τ to be discrete. This process corresponds to summation of columns in the display (Gerstein, 1961).

Scaled interval histograms (Halliday, 1955) for the intervals between every $2^{m\text{th}}$ spike can be written in a way that resembles ordinary interval histograms:

$$I_2(\tau) = \sum_{k=1}^{N} \delta(t_{2k} - t_{2(k-1)} - \tau) \qquad \text{for} \quad m = 1 \tag{5}$$

$$I_4(\tau) = \sum_{k=1}^{N} \delta(t_{4k} - t_{4(k-1)} - \tau) \qquad \text{for} \quad m = 2 \tag{6}$$

$$\vdots \qquad\qquad \vdots$$

$$I_{2^m}(\tau) = \sum_{k=1}^{N} \delta(t_{2^m k} - t_{2^m (k-1)} - \tau) \qquad \text{for any integer} \quad m \tag{7}$$

The τ may, again, be taken as discrete.

We note that both the ordinary and scaled interval histograms may be considered as terms in a particular expansion of the autocorrelation function of the spike train (Gerstein and Kiang, 1960). There are other, more useful, ways of examining the meaning of scaled interval histograms; these will be shown in a subsequent paper.

The computations that we have discussed can always be obtained for any data but become ambiguous in interpretation unless the data are statistically stationary. We use the term stationary when statistical properties of a short sample of data are independent of the particular choice of sample within a long run. This usage does not exclude short-term variations in statistical properties over time intervals comparable to interstimulus intervals. A simple test of stationarity is to show that the chosen computations do not give widely different results for various samples of data that may be selected from a long run. Fig. 2 shows such a demonstration for interval histograms of one of our units. Since our basic computation is the interval histogram, we have applied this test to each unit that has been studied. The few units that failed to pass this relatively crude test for runs as long as 30 minutes were discarded.

RESULTS AND DISCUSSION

Spike Trains, the Basic Data. Short samples of the data that we shall examine are illustrated in Fig. 3. Each spike train was obtained by isolating a different unit. From these photographs one can observe gross differences in the spike patterns. Thus Unit 261–1 seems to fire in bursts,[1] Unit R–4–10 seems to fire rapidly, almost regularly, with no very long intervals between spikes, etc. It is clear, however, that casual visual inspection will not provide adequate descriptions of the spike trains.

The Interval Histograms. The first computation applied to the spike trains is the interspike interval histogram. Fig. 4 shows such histograms for the four spike trains from which the samples in Fig. 3 were selected. A number of interesting features may be discerned from the shape of these histograms. The histogram for Unit 259–2 appears to be unimodal and asymmetric, with a sharp rise and a slower decay; that of Unit R–4–10 appears to be unimodal, symmetric, and possibly bell-shaped; that of Unit 261–1 appears to be bimodal and asymmetric, while that of Unit 240–1 is unimodal and asymmetric, but on a quite different time scale than that of Unit 259–2.

By matching the interval histograms with the corresponding photographs of spike trains (Fig. 3) one can see that Unit R–4–10 is the unit that fires almost regularly, while Unit 261–1 is the "bursty" unit. The spike trains of Unit 259–2 and Unit 240–1 do not appear to be easily characterizable. The interval histograms of these last two units do appear dissimilar; we shall clarify the differences in the next section.

Replotted Interval Histograms. In order to elucidate the differences between the four interval histograms, the results of the computations may be replotted in special ways. When the histogram of Unit 259–2 is replotted on a semilogarithmic scale, all of the points except those for the lowest intervals fall on a straight line;

[1] Whenever one finds units that discharge in bursts, one must suspect possible motion of the electrode relative to the unit as a result of respiratory movements or arterial pulsation. This may be the case for Unit 261-1, although we have no convincing evidence one way or the other.

the histogram is, therefore, exponential (Fig. 5*a*). The fact that the interval histogram rises rapidly to its mode (at 3 msec.), together with the exponential decay, suggests that the process generating the spike train might be a Poisson process with dead time (Alaoglu and Smith, 1938). To verify this interpretation, it is necessary to establish the independence of successive intervals.

When the histogram of Unit R-4-10 is replotted on a semilogarithmic scale,

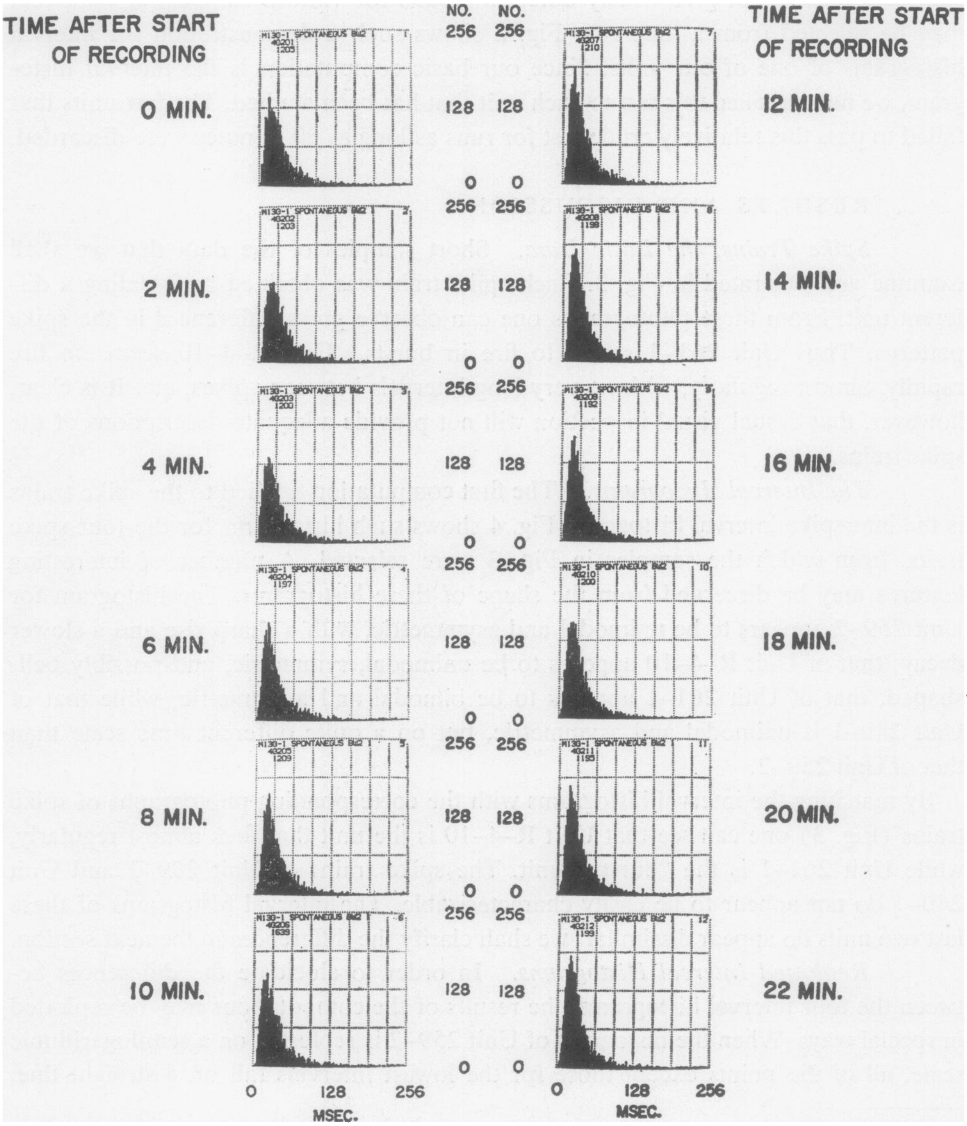

Figure 2 Unit 240-1. Interval histograms of successive 2-minute samples from a half-hour length of data.

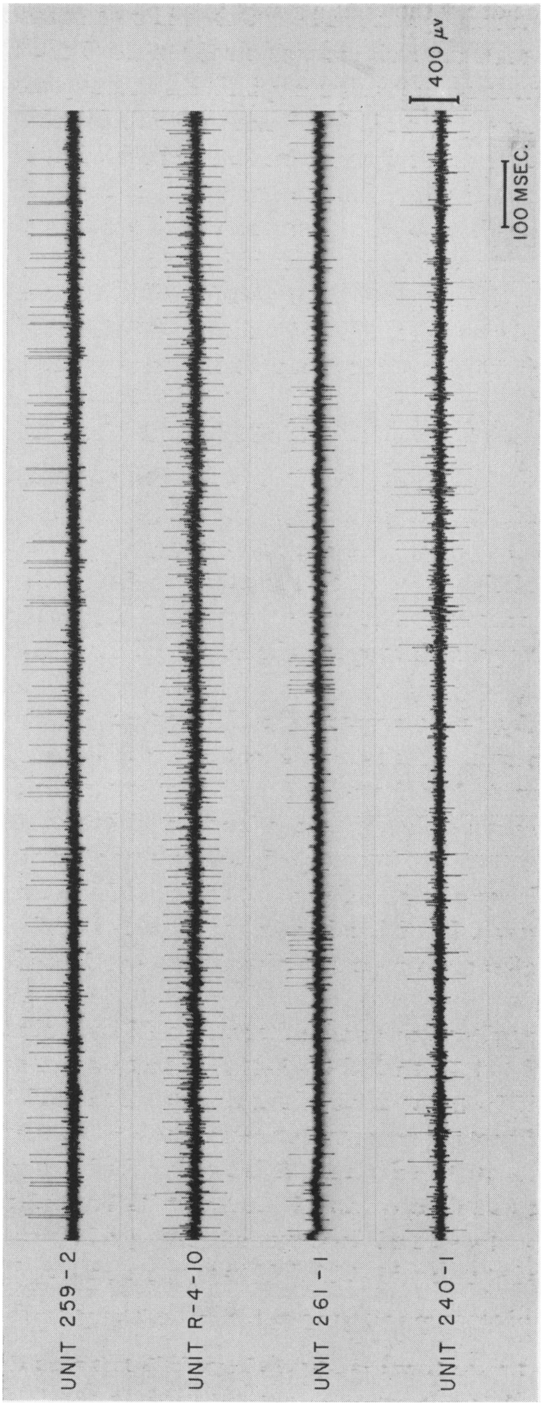

FIGURE 3 Film strips of the spontaneous activity of four selected units.

neither the rise nor the decay shows as a straight-line plot (Fig. 5*b*). The symmetric bell shape, however, suggests replotting on Gaussian density paper. (Onno, 1961). When this is done, as in Fig. 6, a somewhat curved line is obtained. This result suggests that the process generating this spike train is not greatly different from a periodic process with a quasi-Gaussian time jitter.[2] The extent to which successive values

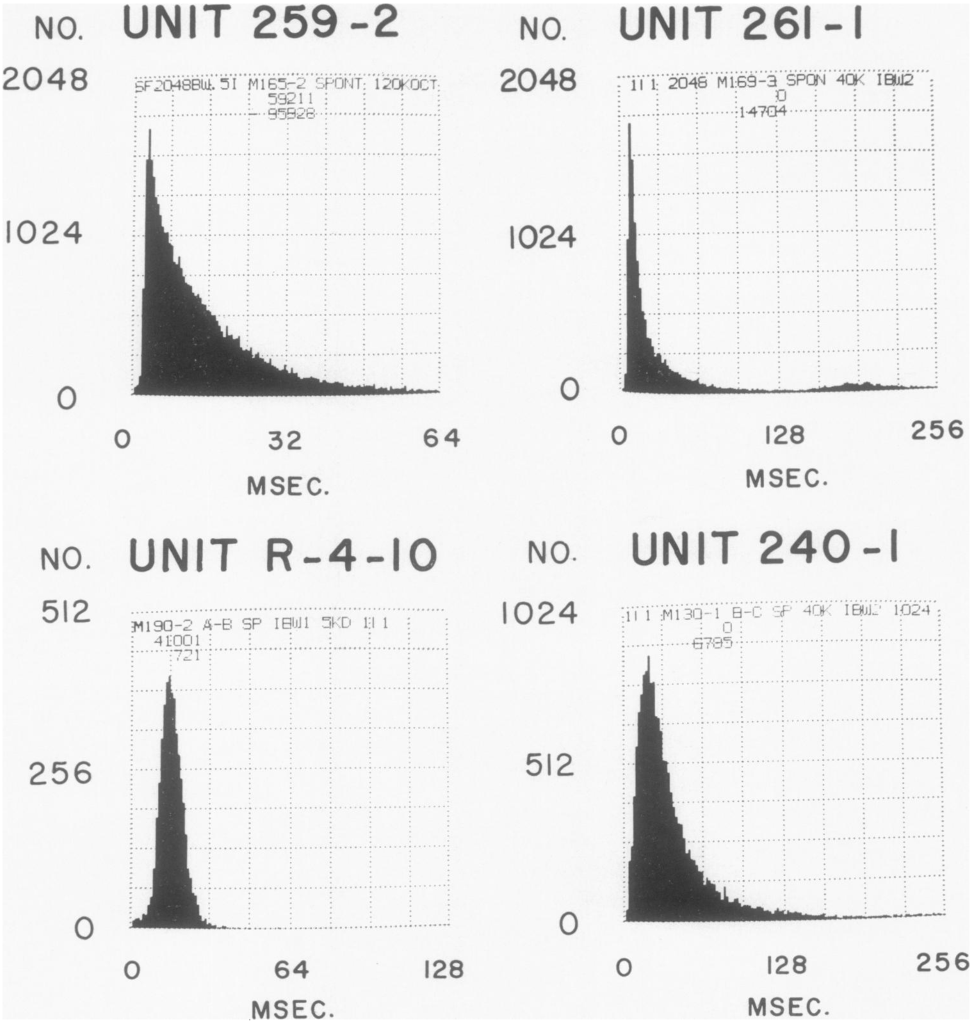

FIGURE 4 Interval histograms for the spontaneous activity of the four units shown in Fig. 3. The number of intervals processed: Unit 259-2, $N = 40{,}960$; Unit R-4-10, $N = 5000$; Unit 261-1, $N = 16{,}384$; Unit 240-1, $N = 16{,}384$.

[2] We shall use "quasi-Gaussian" for a distribution that near its mean is adequately fitted by a Gaussian distribution, but that deviates in the tails.

of the time jitter are statistically independent can be examined by computing the correlation of successive intervals.

Replotting of the histogram of Unit 261–1 on a semilogarithmic scale emphasizes its bimodal aspect (Fig. 5*c*). Such a histogram cannot be the resultant of two steady but different rate processes as, for example, if the activity of more than one unit had been included in the computation. Clearly, the first mode of the histogram at 8 msec. corresponds to the interspike intervals within the bursts, while the second mode at

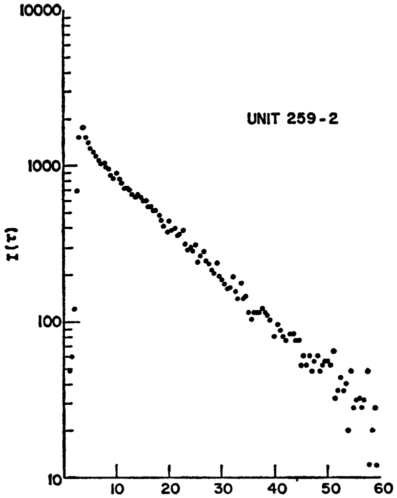

FIGURE 5(*a*)

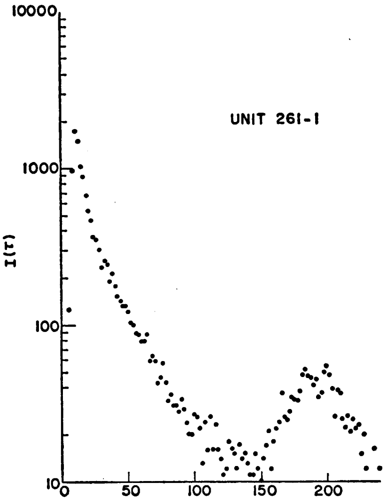

FIGURE 5(*c*)

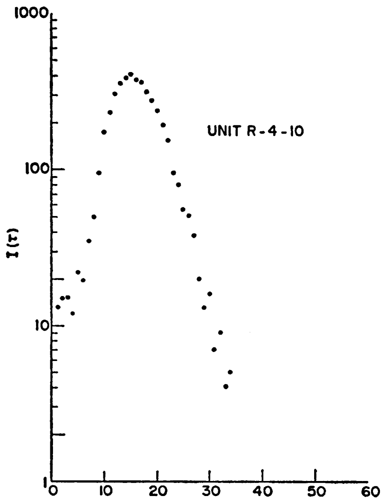

FIGURE 5(*b*)

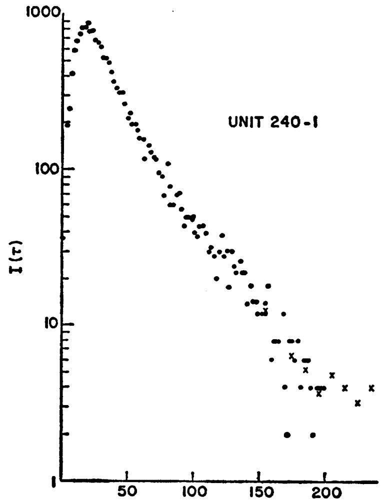

FIGURE 5(*d*)

FIGURE 5 Semilogarithmic replots of the interval histograms of Fig. 4.

approximately 200 msec. corresponds to the interburst intervals. It should be emphasized that the interval histograms cannot be used alone to distinguish between a recurring bursty pattern or a sharp change in the average firing rate of the unit at some time during the data sample. Either the pictures of the spike trains or the stationarity check is also required.

Finally, when the histogram of Unit 240–1 is replotted on a semilogarithmic scale, the decay is clearly seen to be non-exponential (Fig. 5*d*). At this time, we can only characterize the histogram of this unit as unimodal, asymmetric, and non-exponential.

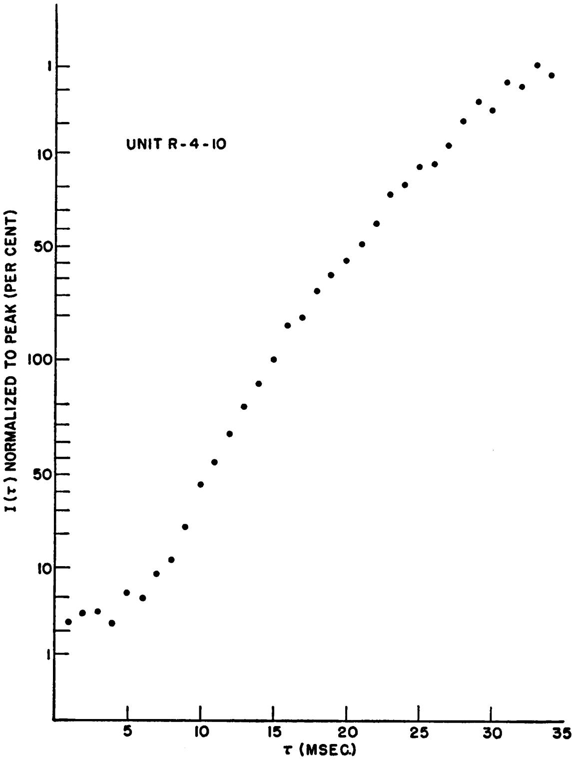

FIGURE 6 The interval histogram of Unit R-4-10 plotted on probability density paper.

Joint Interval Histograms. While the interval histogram gives the range and distribution of time intervals, it does not allow detection of any ordered pattern of intervals.

To study these particular higher-order statistics, we have computed and displayed the joint interval histograms as described in the section on methods. The results of the computations are displayed so that the intensity of each point of the joint histogram represents the number of pairs of intervals which was found with that particular set of values. The joint interval histograms are capable of revealing certain types of recurring time patterns in the spike trains. For example, if there is recurrence of a time interval of short duration followed by one of long duration, the display will show a dark area in the upper left region. If there is recurrence of a long time interval followed by a short time interval, the display will show a dark area in the lower right region. If successive intervals are independent, the joint interval histogram will be symmetric about a 45° line through the origin. This symmetry test is a necessary but not sufficient condition for statistical independence of successive intervals.

The joint interval histogram of the four sample units are shown in Fig. 7. The joint interval histograms of Units 259–2, R–4–10, and 240–1 apparently meet the 45° symmetry test, while the joint interval histogram of Unit 261–1 does not. The joint interval histogram of Unit 261–1 shows dark areas at the upper left and lower right; these show that there is recurrence of a long interval (approximately 200 msec.) preceded by a short interval (8 msec.) and followed by a medium interval (approximately 30 to 60 msec.). There is also a strong tendency for a short interval to be preceded by a short interval and some tendency for a short interval to be preceded by medium or long intervals. These characteristics of the time pattern of the spike train may be easily checked by examining Fig. 3. For a still more systematic study of the spike train, more time-ordering information would be needed. This might be obtained from the order in which a joint interval histogram is filled, or from the joint histogram for non-successive intervals.

For the other three units, a more thorough investigation of statistical independence of sucessive intervals is needed. A definitive proof for statistical independence of successive intervals would be to show that the probability of finding interval 1 followed by interval 2 is just the probability of finding interval 1 multiplied by the probability of finding interval 2, that is,

$$p(1, 2) = p(1)p(2).$$

If, as in most experimental situations, this relationship is not exactly satisfied, it is necessary to estimate the degree of independence. Standard statistical methods can be used (Cramer, 1946) to find the probability that a particular joint distribution be independent. This numerical estimate, however, would not determine the nature of the correlation between successive intervals.

We shall, therefore, substitute another test for independence, which, although less direct, does determine the nature of the correlation. In essence, this test consists of finding the means of each column and each row in the joint interval histogram. Thus we find the mean interval that is preceded (or succeeded) by an interval of a particular given duration. These means are plotted as follows: Column means are plotted *versus* row, and row means are plotted *versus* column. For statistical independence, each set of means will fall on a straight line parallel with one of the axes. This test also is necessary, but not sufficient.

This test for the correlation of successive intervals in a joint interval histogram may be developed in the following way. Consider the numbers found in each column (or row) as an ordinary interval histogram. The numbers in a particular (i^{th}) column, properly normalized, represent the probability density of all of the intervals that are preceded by an interval of the particular (i^{th}) duration. Similarly, the normalized numbers in a particular (j^{th}) row represent the probability density of all of the intervals that are succeeded by an interval of the particular (j^{th}) duration.

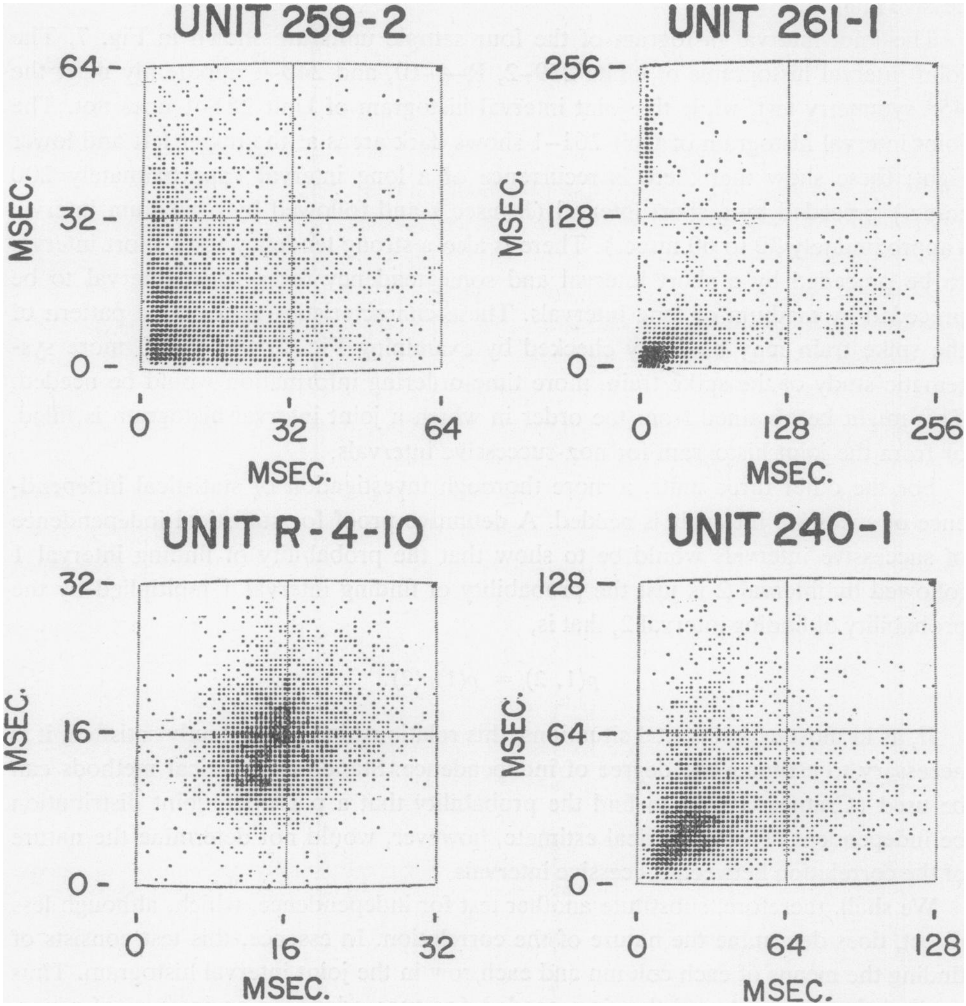

FIGURE 7 Joint interval histograms for the four selected units. Abscissae represent duration of τ_1; ordinates represent duration of τ_2. (See Methods section.) Number of interval pairs processed, $N = 4096$.

In this context, the statistical independence of successive intervals means that the probability density of all of the intervals preceded (or succeeded) by an interval of particular duration does not depend on the length of that particular duration. In other words, with proper normalization, the numbers in every column (or row) should correspond to the same probability density if successive intervals are statistically independent.

Thus our test of independence is reduced to the problem of comparing the probability densities represented by each successive row and column of the joint interval histogram. Two probability densities are the same if they have the same mean, variance, and all higher moments. Thus we may compare the mean, variance, etc. for each successive row and column. Any systematic changes indicate departure from independence and can be directly interpreted.

Constancy of means or variances, etc. represents a necessary condition for independence; sufficiency requires that *all* moments remain constant in this test. In this paper we are discussing applications of this test to only the first moment (mean) of the various probability densities.

Fig. 8 shows the results of such computations for the four joint interval histograms shown in Fig. 7. The row and column means for Unit 259–2 fall on lines parallel to the axes, and thus, support our contention that the discharge pattern of this unit is adequately described by a Poisson process with dead time.

The row and column means for Unit R–4–10 fall on straight lines that are somewhat inclined with respect to the axes. This inclination indicates that there is a weak correlation between sucessive intervals. In the mean short intervals tend to be followed by short intervals, and long intervals by long intervals. Thus the spike train might be generated by a periodic process with quasi-Gaussian time jitter and with some weak correlation between successive intervals.

The row and column means for Unit 261–1 show a distinct difference in their behavior; this is consistent with the asymmetry of the joint interval histogram. Since means of bimodal distributions are extremely poor estimators, we shall not discuss this point in greater detail.

The row and column means for Unit 240–1 fall on a 45° line for intervals less than 30 msec. and on lines almost parallel to the axes for longer intervals. These facts indicate that there is in the mean strong correlation of successive intervals for intervals less than 30 msec., but very little correlation for longer intervals.

This information does not yet permit us to postulate a descriptive model.

Scaled Interval Histograms. With the tests thus far described, a unit such as Unit 240–1 is characterized only by an interval histogram that is unimodal, asymmetric, and non-exponential. Also, Fig. 8 shows that the means of successive intervals are correlated only at small values of interval.

A further test that may have interesting theoretical implications is computation of scaled interval histograms (see Methods). In essence, these are computations of interval histograms for the intervals between every $2^{m\text{th}}$ spike, where m is an integer. In comparing successive orders of scaled interval histograms (successive m), the scales of the ordinates and abscissae are adjusted in the following manner: (a) The vertical scale in N, $N/2$, . . . $N/2^m$. This is necessary because, for a fixed length of total data, each successive order of scaled interval histogram includes only half as many intervals. (b) The horizontal scale is T, $2T$, . . . 2^mT for successive orders of scaled interval histograms. These computations for Units 259–2 and 240–1 are shown in Figs. 9 and 10. The behavior of the two units under this set of transformations is qualitatively different. The scaled interval histogram for Unit 259–2 (Poisson-like process) changes in shape considerably, even for the first transformation.

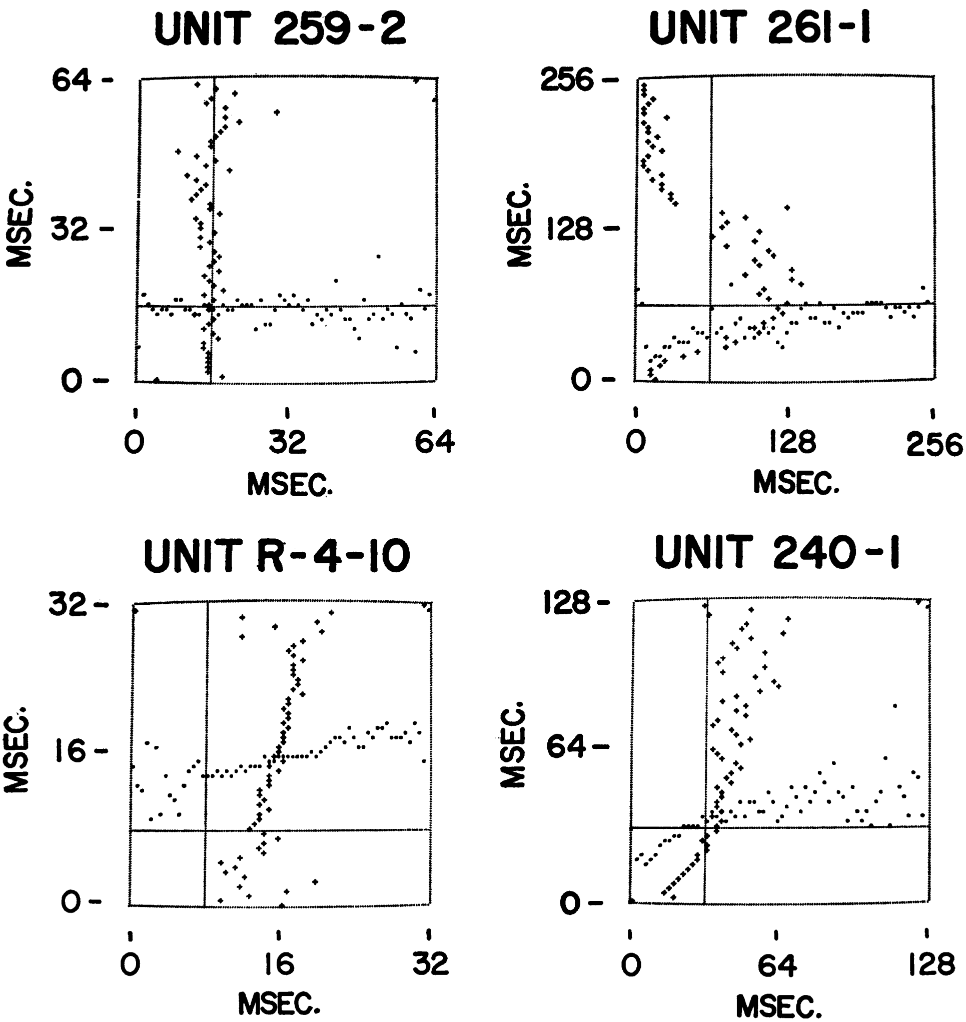

FIGURE 8 Means of each row and column of the joint interval histograms of Fig. 7. Row means (crosses) are plotted against column, column means (dots) are plotted against row.

The scaled interval histogram for Unit 240–1 does *not* change shape appreciably, even for the fourth transformation.

The scaling behavior of Unit 259–2 is consistent with a Poisson-like process (Rainwater and Wu, 1947). The scaling behavior of Unit 240–1 implies a theoretical model that will be described in a subsequent paper.

For Unit R–4–10, scaling is less illuminating, but not inconsistent with the

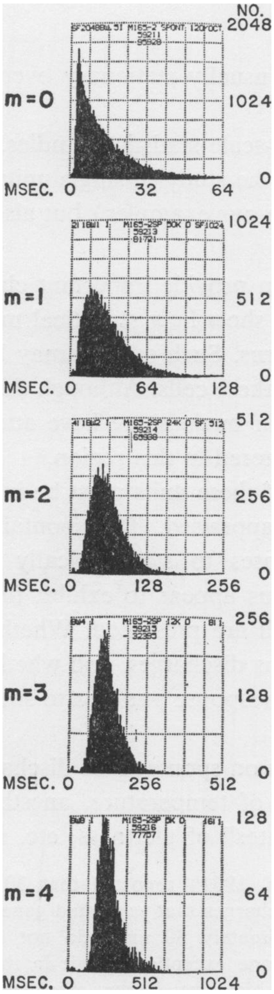

FIGURE 9

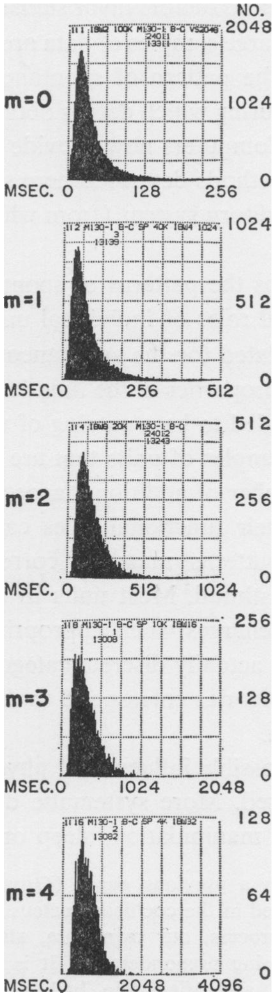

FIGURE 10

FIGURE 9 Scaled interval histograms for Unit 259-2. Note that both vertical and horizontal scales are adjusted by a factor of 2 for each successive order of scaling. $N_0 = 40{,}960$ for $m = 0$; $N_m = N_0/2^m$ for other m.

FIGURE 10 Scaled interval histograms for Unit 240-1. Same scale adjustments as in Fig. 9. Note the approximate invariance of the histogram envelope as m increases.

behavior expected of a periodic process with quasi-Gaussian jitter. As for Unit 261–1, invariance under the scaling transformation is imposible for a bimodal interval histogram.

COMMENTS

We have presented some methods for studying spontaneous discharges of single units. The nature of the data makes any non-statistical description difficult. Several advantageous factors favor statistical study.

(*a*) Large samples of data are easily obtainable.

(*b*) The pattern of spontaneous discharges is usually stationary over the time during which data is obtained.

(*c*) Computers now provide the tools for large-scale statistical studies.

The methods described here seem applicable to the study of single units not only in the auditory system (from which we have drawn our examples) but also in other systems.

Perhaps the patterns of spontaneous activity can provide important clues to the functional roles of individual units. Our examples show how statistical models can be postulated for the spontaneous discharge patterns. Such models may be related to some properties of the functional connections of these cells. Although this paper is not intended to be a catalog of units in the cochlear nucleus, we have attempted to show examples of units that are frequently encountered in this region.[3]

A number of additional aspects of the activity of these units must be investigated before their functional roles can be realistically appraised. The spontaneous discharge patterns must be correlated with responses to systematically presented acoustic stimuli. Most units in the cochlear nucleus appear to exhibit time-locked spike discharges when appropriate acoustic stimuli are presented. Whether or not there are actually discrete categories of spontaneous discharges, and whether or not these categories correspond to different profiles of response patterns to sound is still unknown.

The possible influence of physiological variables on spontaneous discharges must be assessed. More systematic data on the effects of temperature, anesthesia, biochemical manipulation, sleep or wakefulness, "states" of alertness, etc. is needed.

[3] Although a previous paper (Grossman and Viernstein, 1961) reported that 30 out of 31 cells studied in the cochlear nucleus had spontaneous discharges that suggested generation by a Poisson process, our own data, also based on approximately 30 units do not exhibit this overwhelming preponderance. It is interesting that the one exceptional unit in the study by Grossman and Viernstein had a bell-shaped interval histogram. Our own breakdown is approximately: ¼ Poisson, ¼ quasi-Gaussian, several bimodal, several scaling invariant, and ¼ unclassified. In addition many units do not exhibit spontaneous activity and were not included in these numbers. It should be re-emphasized that the meager sampling and inadequate localization of recording site precludes any attempt to deduce the actual numerical distribution of cell types on the basis of these numbers. We have mentioned our proportions only because they differ so markedly from those given by Grossman and Viernstein.

Any or all of these may drastically alter the discharge patterns and, therefore, may need to be carefully controlled, (Brink *et. al.* 1946) (Li, McLennan, and Jasper, 1952) (Li, 1959) (Evarts, 1960).

Finally, the correlation of spontaneous discharge patterns with anatomical knowledge is necessary. It is tempting to inquire whether or not cell types that are distinguishable by histological methods might be correlated with the various types of spontaneous activity.

As the available data on spontaneous activity increase, it is virtually certain that our rather crude analyses will be replaced by more refined techniques. The examples presented here may whet the appetite of theoreticians for more detailed quantitative data.

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